Remarks

Claims 1-54 have been canceled and 64-81 have been canceled. Claims 55-63 and 82 - 86 are pending. Claim 55 has been amended. Basis for this amendment can be found in various places in the specification as filed. For some examples, see paragraphs [00014], [00057], [00058] and [00062].

In connection with the objection to the abstract and figures reiterated in this Office Action, Applicants believe these items were addressed in Applicants' response of December 12, 2006.

Applicants respectfully disagree with the making of the instant rejection final, as Applicant's previous response presented a new claim amendment in claim 83 that the Examiner does not appear to have addressed in the present action.

Claim Rejections - 35 USC § 103

The Examiner has maintained the previous rejection of all the claims under 35 USC 103(a) and deemed the claims to be obvious over Jablonka et al., Archivum Veterinarium Polnicum (1992) Vol. 32, pp 57-66, in view of Stoll et al. Annals N.Y. Accad. Sci. (1994), pp 122-128; Biewenga et al. Gen Pharm (1997) Vol. 29, pp 315-331; Sian et al. Annals of Neurology (1994) Vol 35, pp 348-355, and Kozhenivkova et al. Bull. Experimental Biol. and Med. (1999) Vol. 128, pp 535-537.

In maintaining this rejection, under ***Response to Argument***, the Examiner contends that Applicant's argument that ambroxol alone has no neuroprotective effect is contradicted by the result in Table 2(a). However, Applicants note that the Examiner's argument does not appear to have taken into account the Standard Error of the Mean (SEM) data in the rightmost column of Table 2(a) which permits the calculation that the Control OGD (i.e., the composition containing no ambroxol) has a lower effect range of 12.15, while ambroxol alone has an upper effect range of 12.67, which overlaps with the control range. Therefore, according to the data in Table 2(b), there is **no statistically significant difference** between the neuroprotective effect conferred by the negative control and that conferred by ambroxol alone. Thus, Applicants' statement that ambroxol alone has no neuroprotective effect is indeed correct when viewed in light of the data presented in Table 2(b). Further, the written description of the invention provided in the specification as filed states:

"[T]he important role of thiol-reactive compounds as a protection mechanism in the course of neurodegeneration could be shown by the controlled influence on the cellular thiol/disulfide status by means of two or more substances of the group α-lipoic acid, its salts and isomers and modulators of the glutathione metabolism (ambroxol and its salts and prodrugs and an inhibitor of the ACE)." (See paragraph [0020]).

The application continues:

"Surprisingly, by the combination of two or more substances of the group α-lipoic acid, its salts and isomers, ambroxol and its salts and prodrugs and at least one inhibitor of ACE, the survival of neurons after a neurodegenerative insult could significantly be improved successfully in the experiments described. In contrast to these results, an application of a single one of the above substances had no effect. " (See paragraph [0021]).

Thus, Applicants submit that the lack of a neuroprotective effect of ambroxol alone, or of the other claimed agents acting individually, is adequately supported by the specification as filed. Moreover, such lack of neuroprotective effect of ambroxol, as well as of the other claimed agents acting individually, is corroborated by additional evidence already of record (see Applicants' December 16, 2006 paper enclosing Figures 2, 3, and 4 as appended to the declaration of Dr. Frank Striggow, an inventor on the present application). These data appear to have **again** been disregarded by the Examiner in contending that the combination of agents claimed in the present invention does no more than they would have done individually. Further, the Examiner continues to assert the tautological argument that one skilled in the art would expect the combination used in the method to function in the manner presently claimed because that is what the combination would be expected to do, but offers no evidence as to how or why one skilled in the art would expect the presently claimed synergistic effect, despite Applicants previous submission of extensive arguments and evidence in rebuttal to this position. In connection with this, the Examiner's attention is again drawn to the Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007, which states:

"Once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. All the rejections of record and proposed rejections and their bases should be reviewed to confirm their continued viability. The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings."

In view of this, Applicants **again** request a clear articulation from the Examiner **as to why synergy would be expected by one skilled in the art for the presently claimed method from the cited references**, beyond the erroneous contention that the combination merely performs the same function that each agent performs individually in the claimed method.

Applicants also reiterate over the previously filed responses that the Examiner has asserted (and presently maintains rejections based upon the assertion) that Jablonka et al. and Biawenga et al. teach a composition comprising ambroxile for stimulating GSH, and that Sian et al. teach reduced GSH in Parkinson's disease, and has combined these and the other cited references based on this interpretation of the role of glutathione in cell biology. However, Applicants have previously submitted (and reiterate here) extensive arguments, scientific references and declaratory evidence as to why combining these references against the present application based on the aforementioned interpretation is scientifically and legally inappropriate. To again summarize, the cited references are directed to the oxidative status of glutathione, instead of membrane-bound and intracellular thiol content. In this regard, Applicants believe the record already establishes that there are significant and widely recognized differences between GSH deficiency and thiol-disulfide status, not the least of which differences is the well known fact that glutathione is not representative of total cellular thiols, and in fact that GSH exerts at best a limited influence on the total thiol status of any given mammalian cell. In connection with this, Jablonka et al. only generally discloses ambroxol as anti-oxidative agent, Sian et al. refers to alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders, and Biewenga et al. only disclose the effect of α-lipoic acid on antioxidative properties of cells and on GSH synthesis, **but** none of the references provides information about how to positively influence the total thiol/disulfide status of cells in the central nervous system (CNS). Therefore, a person skilled in the art would have had no motivation to combine the references as the Examiner has done to arrive at the presently claimed method. Furthermore, even if one skilled in the art, upon reading of the alleged GSH stimulatory effects of ambroxile in Jablonka et al., and of reduced GSH in neurodegenerative disorders as in Sian et al., were to test ambroxile for neuroprotective effects, that individual would have observed that ambroxile has no neuroprotective effect when used alone, as demonstrated in Applicants specification as filed and

corroborated by declaratory evidence on the present record. Accordingly, it is submitted that, irrespective of the "historical knowledge in the art of practicing combinatorial medicine" cited by the Examiner, Applicants again point out that it would be illogical for a skilled artisan to continue to combine agents with allegedly known GSH stimulatory properties to eventually achieve even an additive neuroprotective effect because, as should be self-evident, adding one agent with no effect to another agent with similar functional properties would be expected to result in an additive effect of zero.

Notwithstanding the foregoing, Applicants again point out the guidance provided by the Federal Register (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007), which states in connection with rebutting an obviousness rejection:

> "For example, in the case of a claim to a combination, applicants may submit evidence or argument to demonstrate that... the elements in combination do not merely perform the function that each element performs separately."

Applicants accordingly submit the present record provides ample evidence that the presently claimed method does not employ a composition comprising agents that merely perform the same function that each agent performs separately. Moreover, Applicants again reiterate that one must have been able to form a reasonable expectation of success in arriving at the present invention in order to sustain an obviousness rejection. This requirement has not been modified by the *KSR* decision and remains a requirement for a showing of obviousness under both the guidance provided by the MPEP and the Federal Circuit. Further, it is also still a requirement that a reasonable expectation of success not be based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Therefore, Applicants submit that the record in the present case does not present a *prima facie* case of obviousness, and even assuming that it could be argued that such a case has been presented (an assumption Applicants do not make) it is submitted that that case has been rebutted and that the presently pending claims are in condition for allowance.

If the Examiner intends to maintain the present rejections in view of the foregoing remarks, **the Examiner is requested to provide a scientific rationale as to how one skilled in the art would have a reasonable expectation** of achieving a synergistic improvement in the survival of neuronal cells after oxygen and/or glucose deprivation, as presently claimed, beyond

the ongoing conclusory assertion that the compositions claimed in the method of the invention merely perform the same function they do individually, which Applicants submit is incorrect. If no such explanation is provided and the rejections are maintained, Applicants intend to request an Appeal conference.

Conclusion

Based on the arguments and amendments presented herein, Applicants believe all the pending claims are now in condition for allowance and respectfully request the Examiner to allow all the claims. A Request for Continued Examination and a check for the required fee is enclosed. Applicants request a three-month extension of time to file this response. Please charge any additional fees due or credit any overpayment to deposit account number 08-2442.

Respectfully submitted,
Hodgson Russ LLP

By _____
John D. Lopinski, Reg. No. 50,846

The Guaranty Building
140 Pearl Street, Suite 100
Buffalo, NY 14202-4040
Tel:(716) 848-1430
DATE: June 30, 2008